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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/943,075	08/30/2001	Steven N. Popoff	71369.262 and PFI-015	7695

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EXAMINER	
PRIEBE, SCOTT DAVID	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/943,075	POPOFF ET AL.	
	Examiner	Art Unit	
	Scott D. Priebe	1632	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,9,14,16,27,29-31,40,41 and 47-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *9* is/are allowed.

6)☒ Claim(s) *1,2,5,16,27,29-31 and 47-52* is/are rejected.

7)☒ Claim(s) *14, 40, 41* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant filed two preliminary amendments received by the PTO on the dates indicated in the preceding Office action. The first, prepared by Applicant on 1/7/02 and received by the PTO on 1/29/02, amended the specification. The second, prepared by Applicant on 1/29/02 and received by the PTO on 2/12/02, amended the claims.

The Popoff declaration under 37 CFR 1.132 filed 7/28/03 is sufficient to overcome the rejection of claims 1, 2, and 4 based upon Xu et al. The rejections of claim 16 over Strachan and Sanicola-Nadel have been obviated by amendment.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification of in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

Claim Rejections - 35 USC § 101 & 112

Claims 1, 2, and 5 remain and claims 47-52 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. These claims are directed to "a

nucleic acid molecule separated from its natural source". The claims recite limitations on the structure, but not the form of the nucleic acid molecule, e.g. isolated as defined on page 4. The specification as originally filed does not describe to "a nucleic acid molecule separated from its natural source" (see rejection under 35 U.S.C. 112, first paragraph, *infra*). It describes nucleic acid molecules being separated from other molecules present in the natural source, and isolated nucleic acids. A rat cell separated from its natural source, the rat, contains genomic nucleic acid that encodes SEQ ID NO: 2 operably linked to a regulatory region. By extension, the nucleic acid is also separated from its natural source, the rat. Examples of such cells and their nucleic acid "separated from their natural source, i.e. the rat, are lymphocytes cells contained in blood lost by a rat due to a cut; epidermal cells contained in shed hair follicles or in dandruff or sputum; or sperm ejaculated by a male rat. This rejection would be overcome by amending the claims to indicate the hand of man, e.g. by claiming "an isolated nucleic acid molecule".

Claims 1, 2, 5, and 47-52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to "a nucleic acid molecule separated from its natural source". Applicant points to the last paragraph of page 4 for support. However, the specification as originally filed does not describe to "a nucleic acid molecule separated from its natural source." It describes nucleic acid molecules being separated from other molecules present in the natural

source, and isolated nucleic acids. As indicated in the preceding rejection, the claims read on subject matter distinct beyond that described on page 4. There is no evidence of record to indicate that Applicant had contemplated the genera instantly claimed. This rejection would also be overcome by claiming an "isolated nucleic acid molecule".

Claims 16, 27, 30 and 31 remain and claim 29 is rejected under 35 U.S.C. 112, first paragraph, for the reasons of record set forth in the Office action of 4/25/03 as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant's arguments filed 7/28/03 have been fully considered but they are not persuasive. The original grounds of rejection were directed to two different issues. The first issue (pages 4-9 of the Office action) was the over-breadth of "nucleic acid molecule encoding an osteoactivin protein." This issue has been overcome for claim 16 by amendment. Applicant has not addressed this issue with regard to claims 27 and 29-31, which remain rejected on this grounds.

The second issue concerned whether the specification enabled the implied therapeutic use of the composition of claim 16 and the therapeutic method of claims 27, and 29-31. With respect to the hypothesis that administering nucleic acid encoding osteoactivin would stimulate bone formation, Applicant argues that it is not possible to determine whether osteoactivin has a role in bone differentiation from Weterman, Sanicola-Nadel or Anderson because the bone cell differentiation was not considered, and cannot be construed as evidence that osteoactivin is not

involved in bone differentiation. The Examiner concurs with this assessment, and had stated in the rejection that the results presented in these references "do not preclude Applicant's hypothesis." However, these results do show that whatever physiological functions osteoactivin has, they are not limited to involvement in bone differentiation, which raises questions as to what effects other than a hypothetical stimulation of bone formation would result from administering nucleic acid encoding osteoactivin to a mammal *in vivo*. Also, a failure to observe osteopenia in the DBA/2J mice raises doubts as to whether administration of exogenous nucleic acid encoding osteoactivin to a mammal would result in increased bone formation.

Applicant asserts that the specification provides evidence that osteoactivin can stimulate bone differentiation. However, as explained in the rejection, this assertion over reaches the results presented in the specification. Applicant asserts that publications by Safadi and Hadjiargyou also support Applicant's hypothesis. However, copies of these articles have not been made of record, and their contents cannot be considered. Finally, Applicant provides a copy of a manuscript (Appendix A) and alleges that it supports the hypothesis. However, Applicant has provided no evidence attesting to the veracity of its contents, and no evidence as to when the authors became aware of the results presented therein. Applicant is reminded that the enablement requirement pertains to what the specification teaches and what was known in the art at the time the application was filed, not what was known years later.

With respect to the results reported in the manuscript, the Examiner agrees that the evidence suggests a role for osteoactivin in osteoblast differentiation. As to whether the role is critical, the results fail to address that issue. The experiments presented therein involved the use of cultured osteoblasts or osteoblasts-like cells. The experiment testing the effects of exogenous

nucleic acid encoding osteoactivin were performed with cells chosen for their reduced level of osteoactivin as compared to normal primary osteoblasts. Such cells have been removed from their natural environment, and are not exposed to the range of stimuli to which osteoblasts *in vivo* are exposed. While osteoactivin function may be critical for osteoblasts differentiation under the culture conditions employed, it does not follow that it is critical *in vivo*. The authors recognized this distinction in the first sentence of the penultimate paragraph and in the last sentence of the discussion where they state "osteoactivin plays a critical role in osteoblast differentiation in vitro." Furthermore, the phenotype of DBA/2J mouse suggests osteoactivin is not critical for osteoblasts differentiation *in vivo*, as least for mice. Finally, none of the evidence addresses the issue at hand, whether administration of exogenous nucleic acid encoding osteoactivin to a mammal would induce bone formation in any clinically relevant manner.

Applicant asserts that several successful examples of clinical trials existed before Applicant's filing. Applicant points to Verma, page 242. However, this section does not report any success in gene therapy, and specifically addresses the "example" that is the subject of Blaese, Bordignon, and Onodera, and why example has not unequivocally shown successful gene therapy. Also, see Orkin at page 15, and Verma, on page 239, which states "[A]lthough more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story". Furthermore, Blaese, Bordignon, Onodera, Grossman and Lee are all directed to *ex vivo* gene therapy, which has different technical considerations than the *in vivo* gene therapy being claimed. Also, the diseases being targeted and the genes being used are not related to the claimed invention. As disclosed in Orkin, treatment of each specific disease and the methods used to treat them presents

its own set of scientific and clinical challenges (first point on page 1). Thus, one cannot extrapolate from one specific example of gene therapy to determine what would be effective in a different application. Finally, Lee was published well after the effective filing date of the instant application, and cannot be used to support enablement of the instant specification.

Applicant asserts that pages 34-36 of the specification provide one of ordinary skill in the art guidance as to target cells and delivery of nucleic acids. The Examiner respectfully disagrees. This disclosure does no more than provide laundry lists of components for compositions and possible routes of delivery. None of this "guidance" addresses the art recognized problems in gene therapy or the means to overcome them.

Allowable Subject Matter

Claims 14, 40 and 41 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. These claims had been improperly indicated as being allowed. If the suggested amendments to claims 1, 2, and 5 are adopted, claims 1, 2, 5, and 47 –52 would be allowable, claims 9, 14, 40, and without

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (703) 308-7310. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on 703 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Scott D. Priebe

Scott D. Priebe
Primary Examiner
Art Unit 1632